RPD- the rapidly progressive dementia

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Objectives of the presentation

- At the end of the session, the participant will be able to:
- Describe rapidly progressive dementia (RPD)
- Distinguish the different etiologies of RPD
- Prescribe the appropriate workup for a RPD

Plan

- Definition of RPD
- Overview of RPD
- Differential dx
- Clinical approach to dx
- Prognosis
- Some RPD etiologies to remember
- Conclusions
- Questions

I must progress rapidly!

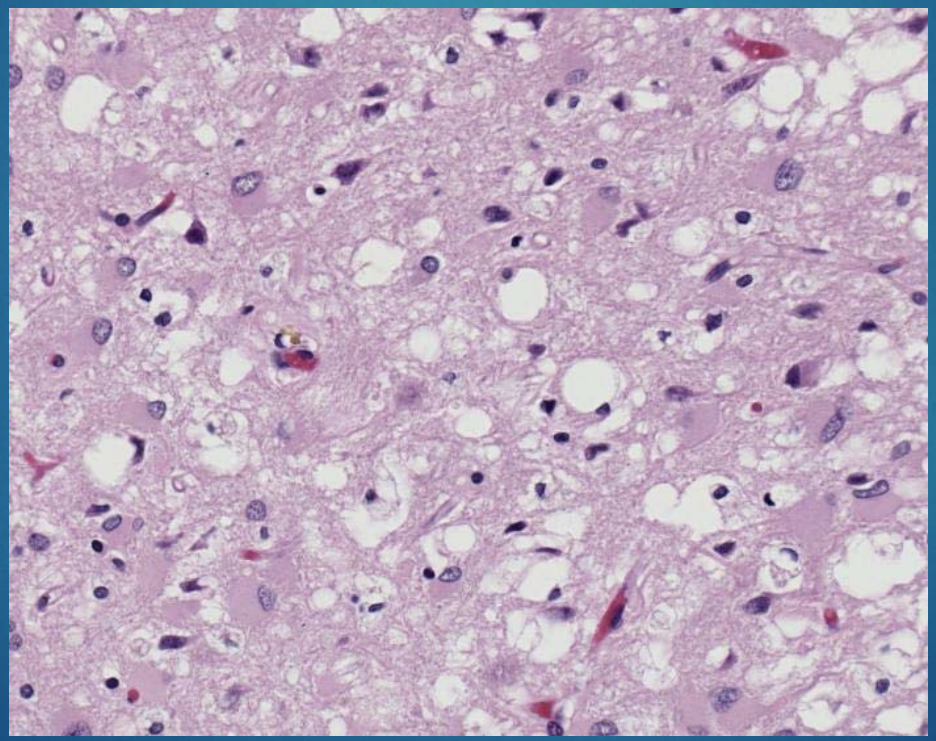
How do you define a RPD?

- A. A dementia that appears within 6 months of first cognitive sx
- B. A dementia that appears within 1 year of first cognitive sx
- C. A dementia that appears within 2 years of first cognitive sx
- D. An already diagnosed dementia that progresses more rapidly than expected

Definition of RPD

- No specific diagnostic criteria !
  - from cognitive "normality" to definite dementia within a specified time: in published studies, where a definition is offered, this time period varies from 3 – 24 months or even longer (4 years!)
- In general, defined as:
- A condition that progress from the first symptom to dementia in less than 2 years, often less than 1 year (UCSF, CCCDTD)
- Or…a person with dementia that is declining at an accelerated rate that is not commensurate with the usual course of the disease

What is the main dx to rule out?



Rapid approach to ddx

- Prion diseases highest in the ddx
  - The most frequent RPD in specialized clinics (up to 76%)…referral bias
  - May lead to death within few months
  - Always think about it…particularly in a patient with prominent motor and/or cerebellar dysfunction
- Some neurodegenerative d/o may be misdiagnosed as CJD
  - FTD-MND: relatively rapid progression, diffuse sx (cognitive, bulbar and motor)
  - CBD and DLB: sometimes accelerated time course; myoclonus and extrapyramidal findings frequent

Rapid approach to ddx

- Atypical presentations of other neurodegenerative disorders:
  - corticobasal degeneration (CBD)
  - frontotemporal dementia (FTD)
  - FTD with motor neuron disease (FTD-MND)
  - DLB (dementia with Lewy bodies)
  - rare cases of AD
- Curable disorders: autoimmune encephalopathies, some infections, neoplasms or metabolic d/o
- Slow course over several years that has been unnoticed or undiagnosed until a rapid decline occurs *R/O delirium

But that's not all ! VITAMINS mnemonic…

- **V**ascular
- **I**nfectious
- **T**oxic-Metabolic
- **A**utoimmune/Inflammatory
- **M**etastases/Neoplasms
- **I**atrogenic
- **N**eurodegenerative
- **S**eizures/Structural/Systemic

Vascular etiologies

- Stroke (multiple, strategic)
- CADASIL (Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy)
  - hereditary stroke disorder; age 40-50; migraines, TIA, CVA
- CAA (Cerebral Amyloid Angiopathy)
  - lobar hemorrhage; focal si/sx, headaches
- Dural arteriovenous fistulas
- Cerebral venous sinus thrombosis
- Thrombotic thrombocytopenic purpura
- Hyperviscosity syndromes/paraproteinemias (polycythemia, monoclonal gammopathies)
- Vasculitis (giant cell arteritis): via infarcts (MID) or glucocorticoid-responsive
- Hypoxic-ischemic encephalopathy

Infectious etiologies

- Viral encephalitis: think about HSV, also WNV, VZV
- HIV dementia
- Progressive Multifocal Leukoencephalopathy (PML)
  - JC virus, immunosuppression
- Subacute sclerosing panencephalitis (SSPE)
  - Measles, children-young adults
- Fungal infections
  - immunosuppression e.g., CNS aspergillosis (also Coccidioides, Histoplasma, Cryptococcus, Blastomyces)
- Syphilis
- Whipple's Disease (bacterium Tropheryma whippelii)
- Rare etiologies: Lyme, balamuthia (ameba → GAE (Granulomatous Amebic Encephalitis)), parasites (toxoplasmosis, trypanosomiasis)

Toxic-Metabolic etiologies

- Vitamin B12 , Vitamin B1 (thiamine), Vitamin B3 (niacin) deficiencies
- Uremia (uremic encephalopathy)
- Electrolyte abnormalities
- Portosystemic encephalopathy/hepatic encephalopathy
  - Acquired hepatocerebral degeneration *EPS
- Bismuth toxicity
- Lithium toxicity
- Heavy metals (Mercury, Arsenic, Lead, Manganese) toxicity
- Alcohol toxicity
- Wilson's disease (Cu), Hallervorden–Spatz syndrome (Fe)
- Endocrine Abnormalities: Thyroid/ Parathyroid disturbances, Adrenal dz
- Hyperglycemia/hypoglycemia
- Genetic disorders of metabolism: Kuf Disease, Methylmalonic Acidemia, Mitochondrial encephalopathies (e.g. MELAS), etc.
- Porphyria

Autoimmune/Inflammatory

- Hashimoto's Encephalopathy (HE)
- Paraneoplastic limbic encephalopathy (PLE)
- Non-paraneoplastic autoimmune (e.g., anti-VGKC encephalo
  NMDA-receptor encephalopathy (NMDARE)…related (or not
  ovarian teratoma)
- Lupus cerebritis
- CNS vasculitides
- Sarcoidosis
- Sjögren syndrome
- Behçet's dz
- Multiple sclerosis
- Celiac disease
- Acute disseminated encephalomyelitis (ADEM)
  - Often following viral infection or vaccination; mostly in children

Metastases/Neoplasms

- Primary CNS neoplasms
- Non-autoimmune paraneoplastic conditions
- Metastases to CNS: breast, lung, RCC, CRC, melanoma
- Metastatic encephalopathy
- Primary CNS lymphoma
- Intravascular lymphoma
- Lymphomatoid granulomatosis
- Gliomatosis cerebri
- Carcinomatous meningitis

Iatrogenic/idiopathic etiologies

- Long list of Rx with anticholinergic properties *delirium
- Cerebral pontine myelinolysis
- Insulin-induced hypoglycemia
- Chemotherapy (methotrexate, 5-fluorouracil, cisplatin, cyc
  A, tacrolimus, levamisole)
- Radiation therapy
- Illicit drug use
- Posterior reversible encephalopathy syndrome (PRES) secondary to kidney failure, eclampsia, malignant HTN, immunosuppression…
- Normal pressure hydrocephalus

Neurodegenerative etiologies

- Creutzfeldt-Jakob disease (CJD): sporadic, iatrogenic, familial
- Frontotemporal dementia (FTD): FTD-MND, bvFTD, PPAs (semantic and non-fluent variant)
- Dementia with Lewy Bodies (DLB)/ Parkinson's disease dem (PDD) and other Parkinson plus syndromes
  - Corticobasal degeneration (CBD)
  - Progressive Supranuclear Palsy (PSP)
- Alzheimer's disease (AD)
- Rare: Neurofilament inclusion body disease, progressive subcortical gliosis

And finally the S… for Seizures/Structural/Systemic

- Epilepsy
- Nonconvulsive status epilepticus
- Subdural hematoma
- Hypertensive encephalopathy

Clinical approach to dx

- The first step in evaluating a patient with RF
  to rule out

…a delirium, as:

- This condition may persist for months
  - In older hospital patients, delirium appears to persist in 44.7% of pati
    at discharge and in 32.8, 25.6 and 21% of patients at 1, 3 and 6 months,
    respectively (Cole MG, *Curr Opin Psychiatry* 2010)
- An underlying cognitive decline is often
  unmasked by delirium

Clinical approach to dx

1- The History

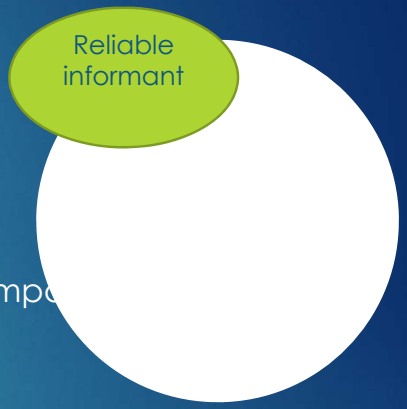
2- The Physical/Neurological Examination

3- The Diagnostic Studies

4- The Brain Biopsy…?

The History

- Premorbid baseline, educational & occupational hx
- PMHx, FamHx, Rx (anticholinergic!), Habits
  - FHx: fCJD, Huntington, mitochondrial encephalopathy, leukoencephalopathy
  - R/O toxic exposures, travels, at-risk sexual hx
- Nature of sx: affected cognitive modalities, functional impa
  psychiatric sx
- Time course:
  - relapsing-remitting: DLB, HE, NMDARE
  - fulminant: sCJD
- Look for c/o motor dysfunction (corticospinal, basal ganglia or cerebellar)
- Systemic sx, weight loss, sx suggestive of CA



The Physical/Neurological Exam'

- Cognitive testing… MMSE/MoCA
  - Cortical-related deficits (apraxia, aphasia or neglect) in CJD
- Mood/affect Δ (CJD, PLE, FTD±MND, VGKC-E, NMDARE, Sy
  - depression, anxiety, apathy, hallucinations…
- CN:
  - oculomotor abnormalities (PSP, CBD)
  - abnormal pupils in neurosyphilis (…)
  - funduscopic exam to R/O ↑ intracranial pressure
- Motor:
  - Asterixis in metabolic encephalopathy
  - Myoclonus (w or w/o startle) in ND dz (CBD, DLB, CJD), toxic-metabolic etiologies
  - EPS in Wilson's, CJD, DLB, PSP, CBD, lesions involving basal ganglia

The Physical/Neurological Exam'

- Others:
  - Frontal release signs frequent in RPDs
  - Cerebellar abnormalities in CJD
  - PNP in toxic-metabolic etiologies
- Above as per neurologists…
- Of course, general physical exam' !
  - HTN, murmurs, signs of PVD for vascular etiologies
  - Fever ± meningismus with some infections
  - Weight loss, lymph nodes, suspicious mass for PND or metastasis

The Diagnostic Studies

- First step: CBC, creatinine, lytes (including sodium, calcium, PO4, Mg), glucose, TSH, ESR, CRP, vitamin B12/Hcy/MMA, LFTs (ammonia), urine A&C
- ± others: RPR/VDRL, HIV, anti-TPO and anti-Tg Ab, ANA, RF, paraneoplastic/autoimmune Ab, anti-VGKC, blood smear, studies, copper, ceruloplasmin, additional rheumatological, heavy metals screen

most of the time

- ± spinal tap: opening pressure, inflammatory markers (WBC, Pr, oligoclonal bands, IgG), glucose, CSF bacterial Gram and culture, fungal cx, acid fast bacilli staining, viral PCRs and culture, VDRL, Whipple PCR; 14-3-3 protein, NSE and tau, cytology/flow cytometry, specific Ab (autoimmune/paraneoplastic encephalopathies)

The Diagnostic Studies

- Brain MRI for ALL pts (but you can start with a plain CT!) : T2, FLAIR, DWI, ADC
  - if focal MTL T2 and FLAIR hyperintensities: suspect LE (limbic encephalitis), autoimmune (anti-VGKC, PND) or infectious (HS
  - characteristic images on DWI/ADC and FLAIR in both cortico subcortical regions in CJD
  - ± Gadolinium, MR angiography or CT angio, carotid US, card
- EEG:
  - focal epilepsy or complex partial seizures
  - triphasic waves in hepatic encephalopathy
  - 1Hz spike and waves associated w CJD
  - non specific theta and delta slowing in early CJD and other ND dz
- ± Brain FDG-PET
- ± CA screen (CT chest-abdomen-pelvis ± mammogram, body PET)

The Brain Biopsy ?!

In extreme cases in which dx cannot be confirmed AND

When diagnosis is essential…

Prognosis of RPD

- Variable depending on the underlying cause:
- Toxic-metabolic causes often can be treated
- Infectious or autoimmune/inflammatory processes (includi
  paraneoplastic disease (PND) and Hashimoto encephaliti
  may often be slowed or reversed with steroids and/or
  immunomodulators (methylprednisolone 1 g IV qd, IV Ig, p
  exchange, rituximab or cyclophosphamide…)
- CJD may lead to rapid progression to death within 5-6 months.
  symptomatic/supportive
- Other neurodegenerative dz can sometimes be slowed down with ChEI or memantine
- Tx of cancer (if possible) in primary CNS lesions, paraneoplastic syndrome

Different etiologies to discuss… or to read later!

- Viral encephalitis
- Neurosyphilis
- Some toxic-metabolic encephalopathies
- Hashimoto encephalopathy
- Paraneoplastic limbic encephalopathy
- Creutzfeldt-Jakob disease

Viral Encephalitis

- Meningitis vs. encephalitis?
  - In latter, Δ mental status, motor or sensory deficits, altered behavior and personality changes, speech or movement disorders; seizures in both
  - Lethargy is possible w meningitis, but no abn of cerebral fx
- Always R/O herpes encephalitis (HSV-1)… bad prognosis if untreated!
  - rapid onset of T^0, headache, seizures, focal neurologic signs, impaired consciousness
  - arises in all age groups
  - various cognitive-behavioral syndromes : hypomania, KBS, amnesia
  - MRI is the most sensitive and specific imaging method for HSV encephalitis (temporal lobes)
  - Empirical tx with IV acyclovir

Viral Encephalitis/cont'd

- West Nile virus: the most common cause of proven viral encephalitis in the USA
  - Associated rash and flaccid paralysis (misdx as GBS!)
- Rabies encephalitis:
  - animals and bites
  - hydrophobia, aerophobia, pharyngeal spasms
- Mumps
  - look for parotitis!
- Uncommon causes: varicella zoster virus (w or w/o zoster), Epstein-Barr virus, HIV, human herpes virus-6, Zika virus
- No specific therapies for most CNS viral infections

Neurosyphilis

- Recrudescence of syphilis, even in the aged persons
- Inflammation: meninges → arteries → CN → spinal roots → brain parenchyma and medulla
- Neurological manifestations can be present in all 3 stages
- Dementia most common in tertiary syphilis
- 5-30 years after infection
- Atypical cognitive and psychiatric presentation
- Personality changes, hallucinations
- Associated neurological signs: Argyll-Robertson pupils, tabes dorsalis, vertigo, gait d/o

Toxic-metabolic encephalopathies

- Bismuth toxicity
  - From overuse of Pepto-Bismol ® !
  - Can be mistaken as CJD
  - Apathy, mild ataxia, tremor, h/a → myoclonus, dysarthria, severe confusion, hallucinations (auditory and visual), seizures… even death
- Lithium toxicity
  - Acute or acute/chronic: late penetration of CNS w delayed confusion, agitation, ataxia, coarse tremors, fasciculations, myoclonus
    - If severe intox: sz, non convulsive *status epilepticus*, encephalopathy
    - SILENT (Syndrome of Irreversible Lithium Effectuated Neurotoxicity) possible despite dialysis
  - Chronic: gradual onset of same sx, with Δ cognitive abnormalities

Hashimoto encephalopathy

- Rare but probably under-diagnosed, treatable; mainly in ♀
- Autoimmune disorder associated w chronic lymphocytic Hashimoto's thyroiditis
- Often begins w prodrome of depression, personality Δ or psychosis
- Then cognitive ↓ associated with myoclonus, ataxia, pyramidal and extrapyramidal signs, stroke-like episodes, ↓ LOC, confusion, seizures
- Overlapping clinical profile with CJD (with HE: more seizures and more fluctuating course)
- Patients may be euthyroid, hypothyroid and hyperthyroid… although Dx cannot be made until a patient is euthyroid.
- ↑ of either anti-thyroglobulin or anti-thyroperoxidase (anti-TPO)
- Tx: immunosuppression; start w high-dose Solumedrol

Paraneoplastic limbic encephalopathy

- Precede the neoplasm in 70% of cases
  - Small cell lung cancer (SCLC) is the most frequent (75%), also: germ-cell tumors (ovarian or testicular), thymoma, Hodgkin's lymphoma and breast CA
- Depression, personality changes, anxiety, emotional lability, irritability and other ψ sx often precede the cognitive dysfunction
- Subacute amnestic syndrome, w short-term anterograde memory ± retrograde amnesia
- Seizures are common
- Anti-Hu is the most common Ab
- Significant neurologic improvement following tumor removal and treatment

Creutzfeldt-Jakob disease

- 3 main types: sporadic (sCJD), familial (fCJD) and variant (vCJD)
- sCJD is the most common (85%)
  - 'Great mimicker' compromising cortical, extrapyramidal and cer
    function with variety of presentation: cognitive, behavioral, sens
    motor (esp. myoclonus) dysfunction; possible constitutional sx
  - Mean age of onset: in 7th decade (range 50 to 70 y.o.), time to d
- fCJD (10-15%)
  - Mutation of PRNP; autosomal dominant
  - Also GSS and FFI
- vCJD
  - Acquired (BSE), young adults (mean 29 y.o.)
  - Psychiatric prodrome > 6 months
  - As sCJD, combination of neurological signs
  - Iatrogenic CJD: another acquired CJD (transplants)

Creutzfeldt-Jakob disease

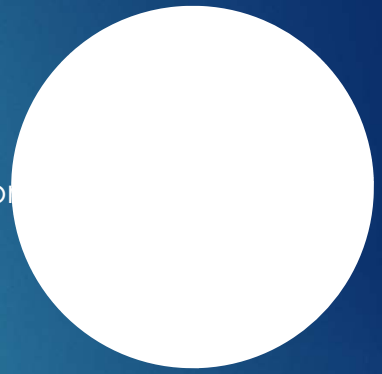
- WHO and CDC criteria for probable sCJD (1998 and 2010):
  - Rapidly progressive dementia +
  - at least 2 of 4 of : myoclonus, pyramidal/extrapyramidal sign
    cerebellar signs, akinetic mutism +
  - positive EEG (periodic epileptiform discharges) and/or positive
    with < 2 yrs of dz duration (and/or ab basal ganglia on MRI *CD
- But…poor Se & Sp of these criteria
  - akinetic mutism and EEG PSWC are found in later stages
  - cerebellar signs, parkinsonism and myoclonus can be seen in other dz
  - behavioral, constitutional and sensory symptoms are frequent but not listed

Creutzfeldt-Jakob disease

- All pts w suspected CJD: CSF, EEG and MRI
  - Typical CSF: mildly ↑ Pr, normal Glu, no WBC; 14-3-3 protein, tau (neuron specific enolase)… all 3 indirect indicators of neurona
    - The future: RT-QuIC (or EP-QuIC) method, which detects PrP^{Sc}
  - EEG: periodic sharp wave complexes (PSWCs): low Se but hig when combined with clinical presentation
  - MRI: relatively sensitive and specific: hyperintensities in neocort (cortical ribboning) and/or deep gray matter (thalamus and/of s on FLAIR < DWI
    - Corresponding hypointensities with ADC : ↑ Sp
    - vCJD: pulvinar sign on MRI
- Definite CJD: brain Bx or autopsy: spongiform changes (not unique to prion dz), abnormal prion pr- (immunohistochemistry)
  - But… not all areas of the brain are affected; no tx available

Conclusion

- DDx for RPD is large
- Common things are common!
- Needs a thorough workup… ideally through hospitalizatio
  step workup is negative



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Thank you!
Questions?